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10/518,503	12/20/2004	Hans-Michael Eggenweiler	MERCK-2957	7857

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ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,503	EGGENWEILER ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19,21,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,21 and 32* is/are rejected.

7)☒ Claim(s) *16,19 and 31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Withdrawal of Indicated Allowability

The indicated allowability of claim 32 is withdrawn to enter the following new ground of rejection.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds prepared in the examples, does not reasonably provide enablement for these compounds:

- Compounds where, in the R3 and R3' definitions, for each of the last 2 recited moieties, the N atom has only 2 valences.
- Compounds where, in the R7 definition, for each of the 10^{th} and 11^{th} recited moieties, the N atom has only 2 valences.
- Compounds where Het is defined as an aromatic heterocyclic ring substituted by carbonyl O.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The specification fails to teach how to make all compounds encompassed by the claims for in which the N atom has

only 2 valences and in which an aromatic heterocyclic ring is substituted by carbonyl O and fails to teach necessary starting materials required to make such compounds encompassed by the claims.

The synthesis of compounds (pages 7-9, *inter alia*) fails to teach commercial availability or how to make starting materials required to prepare the compounds the claims encompass, as defined in the paragraph above. For example, the specification fails to teach commercial availability or how to make starting materials required to prepare compounds in which the N atoms in R3, R3' and R7 each have only 2 valences. Also, the specification fails to teach commercial availability or how to make starting materials required to prepare compounds in which an aromatic heterocyclic ring is substituted by carbonyl O. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make, and thus to use, the invention commensurate in scope with these claims.

Applicants take the position that "the skilled artisan (here: an organic chemist) clearly understands that the remaining bond is substituted by hydrogen," and that "a double bond can be relocated to participate in the carbonyl bond, and still retain the heterocyclic character of the ring." Therefor, Applicants take the position that compounds in which the N atom in R3, R3' and R7 each have only two valences and in which Het is an aromatic heterocyclic ring substituted by carbonyl O are enabled by this specification. The specification must therefore teach how to prepare all such compounds.

Because neither the prior art, nor the present specification nor both together teach how to prepare all of the compounds encompassed by the claims, it follows as a necessary corollary that the method of using these compounds is undisclosed. Unless Applicants can provide reference to all necessary starting materials and procedures required to make all compounds encompassed by these claims, these claims must be limited to the supporting disclosure.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." MPEP 2163, *et. seq*. This application's disclosure is insufficient to enable making certain compounds of claims 1-15, as noted above, based solely on disclosure of compounds of the examples, absent disclosure of a valid method of preparing all claimed compounds as noted in the first paragraph of this rejection above. The state of the art indicates the requirement for undue experimentation.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to meth-

ods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

(1) Breadth of claims.

(a) Scope of the compounds. The claims cover potentially thousands of substituted thiazole compounds.

(b) Scope of the methods of preparing the compounds. The scope of the methods is stated above and below in Point (3) Direction or Guidance. The specification contains insufficient disclosure of the preparation of all claimed compounds. The method scope is discussed above, and the specification does not disclose preparation of all claimed compounds, particularly failing to show the source of the necessary starting materials and intermediates or the methods of preparation of the required starting materials and intermediates.

In *In re Albrecht, et al.,* 185 USPQ 590, 594 (CCPA 1975), claimed compounds were rejected for lack of enablement, because the specification failed to show all necessary starting materials required to prepare all claimed compounds. Appellant attempted to rely on a US patent (Anderson) to show such starting materials. J. Baldwin confirmed that, when appellant's claims are properly rejected as non-enabling for failure to show all starting materials needed to prepare the claimed compounds, appellant must show specifically all such starting materials:

> However, we fail to find all of the missing [starting materials] … necessary to prepare appellants' claimed compounds. … It is incumbent upon appellants to show where in the Anderson *disclosure* one of ordinary skill in the art would glean the necessary information required to satisfy the enablement requirement of the first paragraph of 35 USC 112. The Anderson patent specification contains thirty examples and nine columns of text. Appellants have not pointed out precisely where enablement lies in that disclosure. It is incumbent upon appellants to rebut the assertion that their specification is not enabling.

In re Wands, 8 USPQ2d 1400, 1403 (Fed. Cir. 1988) similarly noted the requirement of the availability of biological organisms when they were necessary starting materials to support enablement of the claims:

> A deposit has been held necessary for enablement where the starting materials … are not readily available to the public. Even when starting materials are available, a deposit has been necessary where it would require undue experimentation to make the … invention from the starting materials. … No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation.

(2) The nature of the invention and predictability in the art: "[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved" and the ability to make all claimed compounds is considered to be unpredictable because all necessary starting materials and intermediates have not been shown to be available. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). In the instant case, the disclosure does not sufficiently address preparation of all claimed compounds.

(3) Direction or Guidance: The specification teaches methods to make certain compounds of the claims, but does not teach methods and required starting materials necessary to prepare all compounds of the claims, as noted above.

Neither the prior art, nor the present specification nor both of them together teach how to prepare all compounds of claims 1-15, as discussed above.

(4) State of the Prior Art: Compound formation is highly species-specific in organic chemistry. *Albrecht* and *Wands*, discussed above, stand as evidence of the prior art acknowledgement that unless starting materials to prepare all compounds within the claimed scope are available, the claims are not enabled. Applicants must show all necessary starting materials or limit the claims accordingly.

(5) Working Examples: The working examples are fully discussed in Point 3) Direction or Guidance, above. Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present,

> The first paragraph of 35 U.S.C. 112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Syst. v. DeKalb Genet., 65 USPQ2d 1452, 1456 (Fed. Cir. 2003). "[T]he scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(6) Skill of those in the art: The state of the art supports that to successfully prepare all compounds, in which the N atom in R3, R3' and R7 each have only two valences and in which Het is an aromatic heterocyclic ring substituted by carbonyl O, requires specific individualized disclosure.

Wikipedia, Valence, http://en.wikipedia.org/wiki/Valence_(chemistry), last modified 10/14/2009, downloaded 10/15/2009, shows that nitrogen has the valence of 3. If Applicants insist that "the skilled … organic chemist … clearly understands that the remaining bond is substituted by hydrogen," they are invited to present a reference verifying that position.

Wikipedia, Keto-enol Tautomerism, http://en.wikipedia.org/wiki/Keto-enol_tautomerism, downloaded 10/16/2009, shows that the aromatic compound, 1,4-dihydroxynapthalene (1), must lose the aromatic nature of the involved ring in order to convert to the corresponding oxo-compound (2).

(7) The quantity of experimentation needed: Based on the disclosure content, one skilled in pharmaceutical arts would have an undue burden to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding making all claimed compounds, as stated above.

Discussion of the above factors demonstrates that the present application sufficiently lacks enablement of the present claims. In view of the claim breadth, unpredictability of methods of making the claimed compounds, one of ordinary skill in this art would undergo an undue amount of experimentation to make the instantly claimed invention commensurate in scope with the claims.

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

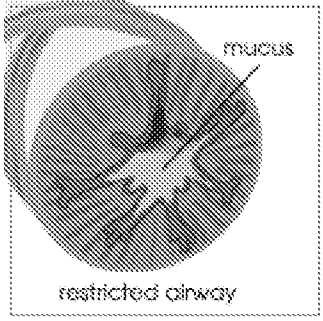
This is a circumstance where the "specification is evidence of its own inadequacy." *In re Rainer*, 153 USPQ 802, 807. All the claimed compounds cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here. Applicants must show making all claimed compounds or limit the claims accordingly.

Claims 21 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treatment of asthma (claim 21) or for inhibition of all cytokine production in human peripheral blood monocytes (claim 32). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. The present specification offers insufficient evidence that the claimed methods treat specific diseases/conditions susceptible to PDE-4 and PDE-7 inhibition amelioration, although the claims encompass treatment of such all forms of asthma. The following reasons apply to this enablement rejection.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is



required: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the methods. The scope of the methods is the use of the trillions of thiazole compounds comprehended under formula I.

(b) Scope of the conditions covered. Asthma is a disease of the lungs that affects bronchial tubes or airways; a reversible obstructive airway disease. Unlike other conditions that obstruct airways, such as cystic fibrosis, chronic bronchitis and emphysema, asthma does not affect sufferers all the time. During an asthma attack, membranes inside bronchial tubes release mucus and become inflamed, causing muscles to contract and create wheezing spasms. Attacks can be severe or relatively mild, but the condition is dangerous and can easily spiral out of control. Specific causes of asthma are far from straightforward. Asthma is divided into a number of different types:

- **Allergic Asthma:** Triggered by allergens, e.g., pet dander, pollen, dust mites, pollutants, wood dust, smoke, irritants, chemicals, viral infections, bacteria, stress, emotion, exercise.

- **Childhood Allergic Asthma:** Maternal smoking can contribute to asthma or other infant lung function impairment, even before a child is born. Continued exposure to cigarette smoking can irritate the respiratory tract, making infants and children particularly vulnerable to allergic asthma.
- **Intrinsic Asthma:** Allergies do not play a part; its typical onset occurs after age 40. Possible causes include respiratory irritants, e.g., perfumes, cleaning agents, fumes, smoke, cold air, upper respiratory infections, gastroesophageal reflux. Intrinsic asthma tends to be less responsive to treatment than allergic asthma.
- **Exercise-Induced Asthma:** Can affect anyone at any age and may be attributed to heat and moisture loss in the lungs with strenuous exercise. Frequent coughing during exercise may be the only symptom, but symptoms can be more severe in cold, dry conditions. Prophylactic medications can prevent onset of asthmatic symptoms for sensitive individuals.
- **Nocturnal Asthma:** Affects people during sleep, regardless of time of sleep. Symptoms can be triggered by allergens in bedding or bedroom, decrease in room temperature and gastroesophageal reflux.
- **Occupational Asthma:** Occurs as a result of breathing chemical fumes, wood dust, or other irritants over long periods of time.
- **Steroid-Resistant Asthma:** Overuse of asthma medications can lead to status asthmaticus, a severe asthma attack that fails to respond to medication and may require mechanical ventilation.

The claimed scope includes treating all forms of asthma, which are inadequately enabled based on PDE-4 and PDE-7 inhibition. The Formula (I) compounds are disclosed to inhibit PDE-4 and PDE-7 and the specification hypothesizes these compounds are therefore useful to treat all forms of asthma noted above for which Appellants provide insufficient competent evidence. Further, Appellants have not provided sufficient competent evidence that the instantly disclosed tests (pp. 21-28, *inter alia*) are highly predictive for all forms of asthma disclosed and embraced by the claim language for the intended host.

Cytokines are any of a number of substances secreted by specific immune cells which carry signals locally between cells, and thus effect other cells. They are a category of signaling molecules used extensively in cellular communication. They are proteins, peptides or glycoproteins. The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin.

Basically, "cytokine" has been used to refer to immunomodulating agents, e.g., interleukins, interferons. Conflicting data exists about what is termed a cytokine and what is termed a hormone. Anatomic and structural distinctions between cytokines and classic hormones are fading as more is learned about each. Classic protein hormones circulate in nanomolar concentrations that usually vary by less than 1 order of magnitude. In contrast, some cytokines (e.g., IL-6) circulate in picomolar concentrations that can increase up to 1,000-fold during trauma or infection. The widespread distribution of cytokine cellular sources may be a feature that differentiates them from hormones. Virtually all

nucleated cells, but especially endo/epithelial cells and resident macrophages are potent IL-1, IL-6 and TNF-α producers. In contrast, classic hormones, e.g., insulin, are secreted from discrete glands, e.g., pancreas. Current terminology refers to cytokines as immunomodulating agents.

Cytokine action may be autocrine or paracrine, but not endocrine, because the signal must be released in the general region of pathogen infected cells, so other immune molecules which follow the signal will arrive at the site where the signal is released. Cytokines are critical to both innate and adaptive immune response development and functioning, although not limited to just the immune system. They are often secreted by immune cells that encounter a pathogen, thereby activating and recruiting further immune cells to increase the system's pathogen response. Cytokines are also involved in developmental processes during embryogenesis.

Each cytokine has a matching cell-surface receptor. Subsequent intracellular signalling cascades then alter cell functions. This may include upregulation and/or downregulation of several genes and their transcription factors, resulting in other cytokine production, an increase in the number of surface receptors for other molecules, or suppression of their own effect by feedback inhibition. The effect of a particular cytokine on a given cell depends on the cytokine, its extracellular abundance, presence and abundance of the complementary cell surface receptor, and downstream signals activated by receptor binding; these last two factors can vary by cell type. Cytokines are characterized by considerable "redundancy;" many cytokines appear to share similar functions.

Function generalization is not possible with cytokines. Nonetheless, their actions may be grouped as autocrine - if the cytokine acts on the same type of cell that secretes it; or paracrine - if the target is restricted to a different type of cells in the immediate vicinity of a cytokine's secretion. Cytokines binding to antibodies have a stronger immune effect than the cytokine alone. Cytokine oversecretion can trigger a dangerous syndrome known as a cytokine storm.

Cytokines have been classed as lymphokines, interleukins and chemokines, based on their presumed function, cell of secretion or target of action. Cytokines are characterized by considerable redundancy and pleiotropism.

- Researchers initially used the term *interleukin* for cytokines whose presumed targets are principally leukocytes. It is now used largely to designate newer cytokine molecules regardless of their presumed function. The vast majority of these are produced by T-helper cells.
- The term *chemokine* refers to a specific cytokine class that mediates chemoattraction (chemotaxis) between cells. IL-8 (interleukin-8) is the only chemokine originally named an interleukin.

Structural homology has been able to partially distinguish between cytokines that do not demonstrate a considerable degree of redundancy so that they can be classified into these types:

- The 4 α-helix bundle family - Member cytokines have 3-dimensional structures with 4 α-helix bundles. This family in turn is divided into 3 subfamilies: IL-2 subfamily; interferon subfamily; and IL-10 subfamily. The IL-2 subfamily is the largest. It contains several non-immunological cytokines

including erythropoietin and thrombopoietin. Also, 4 α-helix bundle cytokines can be grouped into *long-chain* and *short-chain* cytokines.

- The IL-1 family, which primarily includes IL-1 and IL-18.
- The IL-17 family, which has yet to be completely characterized, though member cytokines have a specific effect in promoting proliferation of T-cells that cause cytotoxic effects.

(2) The nature of the invention and predictability in the art:

The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be unpredictable. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance:

The direction and guidance provided is very limited. The dosage range information (p. 83+, *inter alia*) is vague and meager. Even the broadest range is 25 fold. Moreover, this dosage information is generic, the same for the many disorders covered by the specification. There is no specific direction or guidance regarding a therapeutic regimen or dosage effective specifically for various compounds described for various medical conditions comprehended.

In *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 86 USPQ2d 1196, 1202 (Fed. Cir. 2008), Mylan Labs. challenged the enablement of an Ortho-McNeil Pharm. patent. J. Rader noted three specific informative instances of the enabling teachings of the Ortho-McNeil patent there at issue:

> [1] …the average adult requires 30-2000 milligrams of the claimed compounds administered in two to four doses of 10-500 milligrams. [2] The specification also teaches a skilled artisan to use the claimed compounds in a manner similar to the drug phenytoin. [3] Further the specification directs the reader to a reference by L.S. Goodman, which teaches that after establishment of a low initial dose, the dosage is increased at appropriate intervals as required for control of seizures or as limited by toxicity with further adjustments according to plasma drug concentrations. …

(Numbering added.) This specification completely lacks such types of information. Moreover, the dosage is generic; the same for the many asthma disorders the claim covers. Claim 21 construes 7 different types of asthma and claim 32 construes all cytokines mentioned above. The specification fails to provide information, approvingly noted by J. Rader, for present methods in regard to these conditions. *Ortho-McNeil* supports this rejection for lack of enablement.

(4) State of the Prior Art:

Torphy, et al., Environmental Health Perspectives 102, Suppl. 10, Dec. 1994, cautiously state that alleviation of only one symptom was noted in PDE IV therapy: "by virtue of their ability to modify eosinophil function at several levels, PDE IV inhibitors may reduce epithelial cell damage associated with asthma."

Zhu, et al., CNS Drug Rev. 2001 Winter;7(4):387-398, warn, "The clinical use of rolipram [a selective inhibitor of PDE IV] is limited because of its behavioral and other side effects."

Molina, et al., J. Infect. Diseases, 161, #5 (May, 1990), pp. 888-893, show cytokines are produced by peripheral blood monocytes, and "Monocytes/macrophages … are a heterogeneous population of cells at various stages of differentiation, which therefore may have different patterns of cytokine production."

Laso, et al., Cytometry Part B (Clinical Cytometry) 72B:408-415 (2007) anamolously reported:

> [T]he ratio between the spontaneous and stimulated production of IL1β, IL12 and TNFα was significantly reduced in AWLD [alcoholics without liver disease] patients, respectively. Such apparent functional defect of PB [peripheral blood] monocytes from AWLD patients could be related to the increased *in vivo* activation of PB monocytes specifically found in this group of individuals. In spite of our findings in AWLD patients, it should be noted that acute alcohol treatment has been shown to directly inhibit secretion of inflammatory cytokines. Altogether, these observations would support the notion that the effects of acute and chronic alcoholism on the production of inflammatory cytokines by PB monocytes could be paradoxically different.

(5) Working Examples:

The examples show production of a meager number of compounds from among trillions Formula I covers. No *in vivo* biological data is presented. *In vitro* testing is shown only for inhibition of T-cell proliferation and cytokine production control in human PBMCs. Regarding salts and stereoisomers, *Morton Intrntl. v. Cardinal Chem.*, 28 USPQ2d 1190, 1194 (Fed. Cir. 1993) stated:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds … However … there is no evidence that such compounds exist … [T]he examples … do not produce the postulated compounds …

(6) Skill of those in the art: Discussions by Molina and Laso substantiate the need for further inventive research to be able to use the present methods to treat all claim 21 asthma forms. Discussions by Torphy and Zhu substantiate the need for further inventive research to be able to identify the cytokines inhibited by the claim 32 method.

(7) The quantity of experimentation needed:

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding testing types needed to support *in vivo* use. MPEP 2163, *et. seq*. The application disclosure is insufficient to enable instantly claimed methods based solely on disclosure of inhibition of proliferation of T-cells and cytokine production control in human PBMCs by Formula I compounds. Such experimentation is potentially open-ended.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all of the embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." Here, the claims at issue cover treating many conditions and do not enable all of them.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the

embodiments. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." Here, the claims at issue cover treating many conditions and do not enable all of them.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, in the definition of R3 and R3', in each of the last two recited moieties, the nitrogen atom has only two valences. In the definition of R7, in each of the 10th and 11th recited moieties, the nitrogen atom has only two valences. Wikipedia, Valence, http://en.wikipedia.org/wiki/Valence_(chemistry), last modified 10/14/2009, downloaded 10/15/2009, shows that nitrogen has the valence of 3. If Applicants insist that "the skilled … organic chemist … clearly understands that the remaining bond is substituted by hydrogen," they are invited to present a reference verifying that position.
- In claim 1, if Het is an aromatic heterocyclic ring, it cannot be substituted by carbonyl oxygen. Wikipedia, Keto-enol Tautomerism (cited above) shows that the atomatic compound, 1,4-dihydroxynapthalene (1) must lose the aromatic nature of the involved ring to convert to the corresponding oxo-compound (2).

Objected Claim – Allowable Subject Matter

Claim 16, 19 and 31 would be allowable if rewritten to overcome the 35 USC 112, 2nd paragraph rejections set forth in this Office action and to include all limitations of the base claim and any intervening claims. The Office Action of 01-11-2008 has an examiner's statement of reasons for indicating allowable subject matter.

Conclusions

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through

Friday; 8:30 am through 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. If you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia M. Jaisle/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, AU 1624